





CORONARY ARTERY DISEASE

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Original Studies

Comparison of long-term clinical outcomes in multivessel coronary artery disease patients treated either with bioresorbable polymer sirolimus-eluting stent or permanent polymer everolimus-eluting stent: 5-year results of the CENTURY II randomized clinical trial

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Abstract

Objectives: To assess the long-term safety and efficacy of a sirolimus-eluting stent with bioresorbable polymer (BP-SES; Ultimaster), in comparison to a benchmark everolimus-eluting, permanent polymer stent (PP-EES; Xience), in a prespecified subgroup of patients with multivessel coronary artery disease (MVD) enrolled in the CENTURY II trial.

Background: The use of coronary stenting in high-risk subgroups, like MVD patients, is rising. The clinical evidence, including long-term comparative analysis of the efficacy and safety benefits of different new-generation drug eluting stents, however, remains insufficient.

Methods: Among 1,119 patients (intention-to-treat) enrolled in the CENTURY II prospective, randomized, single-blind, multicenter trial, a prespecified subgroup of 456 MVD patients were allocated by stratified randomization to treatment with BP-SES ($n = 225$) or PP-EES ($n = 231$). The previously reported primary endpoint of this study was freedom from target lesion failure (TLF: a composite of cardiac death, target vessel-related myocardial infarction [MI] and clinically-indicated target lesion revascularization) at 9 months.

Results: In this MVD substudy, baseline patient, lesion and procedure characteristics were similar between the treatment arms. At 1 and 5 years, both BP-SES and PP-EES

Abbreviations: (N)IDDM, (non) insulin-dependent diabetes mellitus; (N)STEMI, (non) ST-segment elevation myocardial infarction; ACC/AHA, American College of Cardiology/American Heart Association; ARC, academic research consortium; BARC, bleeding academic research consortium; BP, bioresorbable-polymer; BP-SES, bioresorbable polymer sirolimus-eluting stent; CABG, coronary artery bypass graft; CEC, clinical events committee; CI, confidence interval; CTO, chronic total occlusion; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DMC, data monitoring committee; ITT, intention-to-treat; MI, myocardial infarction; MVD, multivessel disease; PCI, percutaneous coronary intervention; POCE, patient-oriented composite endpoint; PP, permanent-polymer; PP-EES, permanent polymer everolimus-eluting stent; ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization; TV, target vessel; TVF, target vessel failure; TVR, target vessel revascularization

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Funding information

Terumo

displayed low and comparable rates of TLF (5.3 vs. 7.8%; $p = .29$ and 10.2 vs. 13.4%; $p = .29$), and definite or probable stent thrombosis (0.4 vs. 1.3%; $p = .33$ and 0.9 vs. 1.7%; $p = .43$), respectively. Composite endpoint of cardiac death and MI, and patient-oriented composite endpoint of any death, MI, and coronary revascularizations were also similar.

Conclusions: These results confirm good long-term safety and efficacy of the studied bioresorbable polymer stent in this high-risk patient population.

KEYWORDS

clinical trials, complex PCI, coronary artery disease, drug eluting, percutaneous coronary intervention, stent, stent design/structure/coating

1 | INTRODUCTION

In recent years, the use of coronary stenting in high-risk subgroups, like multivessel disease (MVD) patients, has increased. The treatment of MVD patients, by percutaneous coronary intervention (PCI), however, is still challenging. These patients usually have more risk factors and comorbidities (e.g., diabetes), as well as overall less favorable long-term outcomes. Moreover, the PCI in MVD patients is often more complex and associates with higher procedural risk.¹ Choosing the most suitable revascularization strategy for MVD patients requires careful evaluation of both patient and lesion status. The available evidence suggests that in MVD patients without diabetes and/or with low-anatomical complexity, PCI, and coronary artery bypass grafts (CABG) achieve similar long-term outcomes with respect to survival and the composite clinical outcomes. In MVD patients with intermediate-to-high anatomical complexity, however, evidence from large studies implicates CABG as still the preferred choice over PCI in terms of reducing mortality and risk of other serious adverse events.²

The application of antiproliferative drugs onto bare metal stent scaffolds has improved PCI outcomes with respect to restenosis and the need for repeat interventions.^{3,4} Less favorable long-term safety profile, that is, higher risk of (very) late stent thrombosis (ST),⁵ however, challenged these initially promising results. Due to its association with chronic inflammatory reactions, delayed arterial healing, poor re-endothelialisation and positive remodeling,⁶ permanent polymer (PP) coating of first generation drug-eluting stents (DES) became one of the prime targets for redesign. Consequently, several more advanced drug-carriers were developed, including bioresorbable polymeric carriers (BP) and biocompatible PP variants, as well as nonpolymeric stent surfaces.⁷

In the CENTURY II (Clinical Evaluation of New TerUmo drug-eluting coronary stent system in the treatment of patients with coronary artery disease) trial, the Ultimaster sirolimus-eluting BP stent (BP-SES; with abluminal, gradient polymer coating) was shown to be noninferior to the Xience PP everolimus-eluting stent (PP-EES; with

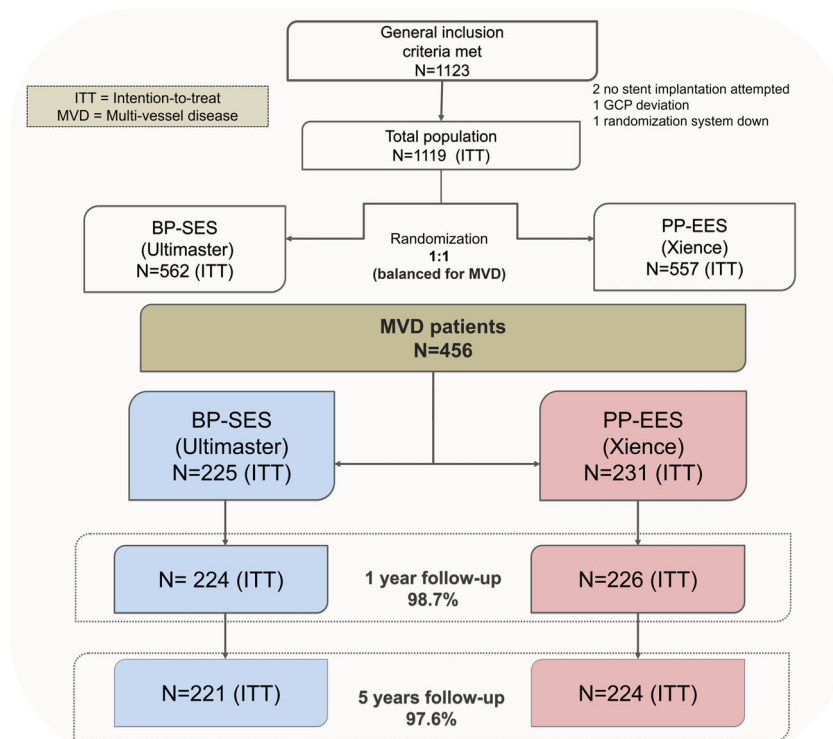
circumferential, biocompatible polymer coating) in terms of freedom from target lesion failure (TLF: a composite of cardiac death, target vessel-related myocardial infarction [MI] and clinically driven target lesion revascularization [TLR]), in total study population, at 9 months follow-up (primary endpoint).⁸ Good clinical performance of the two stents was recently confirmed also for the long-term, 5-year follow-up period.⁹ In this manuscript, we report the 5-year clinical outcomes of a subgroup of the original CENTURY II trial, consisting of patients diagnosed with MVD at the time of randomization.

2 | METHODS

2.1 | Study design and patients

CENTURY II is a prospective, randomized, single-blind, controlled, non-inferiority, multicentre, clinical trial of BP-SES (Ultimaster, Terumo Corporation, Japan) and PP-EES (Xience, Abbott Vascular; study registration number: UMIN000006940), involving 58 enrolling centers (see list in Supporting Information) from Europe, Japan, and South Korea. Out of 1,119 patients, 456 (40.8%) were diagnosed at the time of study entry with MVD and during randomization, that was stratified for this characteristic, allocated to treatment with either BP-SES ($n = 225$) or PP-EES ($n = 231$; Figure 1). MVD was defined as the presence of >50% diameter stenosis in two or three major epicardial coronary vessels or bypass grafts (as measured by caliper method or coronary angiography online). Analysis of this prespecified MVD subgroup was done using the intention to treat (ITT) approach. Detailed CENTURY II study design and methods have been described elsewhere.⁸ In brief, patients with ischemic heart disease due to stenotic lesions of coronary arteries with reference vessel diameter suitable for treatment with stents ≥ 2.5 and ≤ 4.0 mm (≤ 3.5 mm in Japan) were eligible. Patients were randomly (1:1) assigned to PCI with either BP-SES or PP-EES. Randomization was balanced (stratified) for diabetes mellitus, high-risk acute coronary syndrome, and MVD. All patients had to provide a signed written informed

FIGURE 1 Study flow chart. Follow-up rates reflect patients with the completed follow-up visit or those who died during the follow-up period. BP-SES, bioresorbable polymer sirolimus-eluting stent; PP-EES, permanent polymer everolimus-eluting stent [Color figure can be viewed at wileyonlinelibrary.com]



consent. The study complied with the Declaration of Helsinki and was approved at each participating center by institutional review board and competent authority of each participating country.

2.2 | Procedures

All coronary interventions were performed according to standard hospital practice, while all postrandomization procedural decisions were left at operators' discretion. Dual antiplatelet therapy (DAPT) was recommended for at least 6 months. Clinical follow-up was scheduled at 1, 4, 9 months, and yearly until the final 5-year control visit.

2.3 | Data management and quality assurance

A data monitoring committee (DMC) was responsible for the review of all data and identification of potential safety issues. An independent clinical event committee (CEC) reviewed and adjudicated all major endpoint-related adverse and bleeding events. All data on case report forms were 100% verified on-site versus source documents. Members of DMC and CEC were blinded to patient assignment, while investigators and study personnel were not.

2.4 | Study devices

Detailed technical description of the Ultimaster (BP-SES) and its' comparator device Xience (PP-EES) have been previously reported.⁸ Briefly, Ultimaster uses a thin strut (80 μ m) cobalt-chromium platform, with an abluminal gradient bioresorbable polymer coating, while Xience (PP-EES) platform is also based on cobalt-chromium alloy with PP coating.

2.5 | Endpoints and definitions

The primary endpoint of CENTURY II study was freedom from target lesion failure (TLF), a device-oriented composite endpoint consisting of cardiac death, myocardial infarction (MI) not clearly attributable to a nontarget vessel, and clinically driven target lesion revascularization (TLR) at 9-months. Secondary outcomes included (a) rate of target vessel failure (TVF), defined as composite of cardiac death and MI not clearly attributable to a nontarget vessel, and clinically driven target vessel revascularization (TVR); (b) patient-oriented composite endpoint (POCE) composed of all deaths, all MI and all coronary revascularizations; (c) composite of cardiac death and MI (d) rates of cardiac death, MI, TLR, TVR; (e) ST; and (f) rate of bleeding and vascular complications according to Bleeding Academic Research Consortium (BARC) definitions.¹⁰ The endpoints are defined as per Academic Research Consortium recommendations.¹¹

2.6 | Statistical analysis

The CENTURY II randomized trial was statistically powered for non-inferiority of BP-SES compared to PP-EES regarding the primary endpoint of freedom from TLF in the total population at 9-months. The TLF-free rate was 95.64% for BP-SES and 95.09% for PP-EES, demonstrating non-inferiority ($p < .0001$). Both per-protocol and ITT analyses gave similar results.⁸ The present analysis is focused on subset of MVD patients. Here, categorical variables were compared using the chi-squared test (for binary variables) and the Cochran–Mantel–Haenszel test (for multinomial variables). Continuous variables were compared using nonparametric test (i.e., Mann–Whitney for two-group comparisons) or Kruskal–Wallis test (for multiple group

comparison). Dichotomous clinical endpoints were tested using the chi-squared test. The Kaplan–Meier method was used to estimate event rates for time-to-event outcomes, while the data were compared using the log-rank test. To explore whether TLF with BP-SES versus PP-EES was consistent across categories of clinical, procedural, or lesion characteristics, logistic regression analysis with interaction testing was performed. All analyses were performed, using the SAS software, version 9.4 (SAS Institute, Inc., Cary, NC).

3 | RESULTS

3.1 | Patient and procedural characteristics

Four hundred and fifty-six MVD patients were assigned to either BP-SES ($n = 225$) or PP-EES ($n = 231$) treatment-arm (Figure 1). This subgroup constituted 40.8% of the total study population ($n = 1,119$). The mean age was 66 years, with 19% females. A relatively high percentage (35%) of diabetes was observed, but this did not differ between treatment arms. No significant differences in proportion of cardiac risk factors, mean Charlson comorbidity index, nor in the mean SYNTAX score were observed among the two treatment arms. Most of the patients had stable angina, while 27% presented with the high-risk acute coronary syndrome (ST-segment elevation MI [STEMI] and non-ST-segment elevation MI [NSTEMI]). On average patients had 2.3 ± 0.5 diseased vessels of which 1.4 ± 0.5 were treated. Overall, baseline patient characteristics did not differ significantly, aside of the higher frequency of previous smokers in BP-SES arm (Table 1).

Altogether, 738 lesions, 364 in BP-SES and 374 in PP-EES study-arm were treated. Mean number of detected lesions per patient was 3.1 ± 1.4 , of which 1.6 ± 0.8 were subjected to coronary stenting. Lesion localization was similar between the study groups. More than 80% of lesions were classified as type B2 or C (ACC/AHA classification), while 12.7% represented bifurcation lesion. The frequency of ostial localization as well as the level of lesion calcification did not differ between the two treatment arms. Only significantly higher presence of chronic total occlusion (CTO) lesions was noted in BP-SES treated patients (Table 2). Regarding the procedural aspects, the frequency of pre- and post-dilatations, and utilized access sites were similar among the two arms, radial artery being the most frequently used approach (69.1%). Mean total implanted stent number and the total length of the implanted stents per patient were 1.9 ± 1.0 and 37.0 ± 21.3 mm, respectively, and were similar among the two arms. Overall, baseline lesion and procedural characteristics were largely alike (Table 2).

DAPT at each time point (1 month, 4 months, 9 months, 1-year, 2-year, 3-year, 4-year, and 5-year follow-up) is shown in Table 3. Proportion of patients on DAPT did not differ between the two treatment arms during the entire follow-up period.

3.2 | Medium- and long-term clinical outcomes

Throughout 5-year follow-up period, the rate of TLF composite endpoint was similar among the two treatment arms: 5.3 versus 7.8% at

TABLE 1 Baseline patient characteristics

	BP-SES $n = 225$	PP-EES $n = 231$	<i>p</i> Value
Age, years	65.8 \pm 10.4	66.9 \pm 11.3	.31
Male gender	77.8	84.0	.09
Body mass index, kg/m ²	27.3 \pm 4.2	26.8 \pm 4.2	.27
Silent ischemia	16.4	16.5	.99
Stable angina	48.9	42.9	.20
Unstable angina	12.0	9.1	.31
STEMI	4.9	7.4	.27
NSTEMI	17.8	24.2	.09
Diabetes mellitus,			
IDDM	21.4	18.2	.61
NIDDM	78.6	81.8	.61
Dyslipidemia	71.0	71.1	.99
Hypertension	74.1	71.2	.49
Smoker, current	19.6	24.3	.23
Smoker, previous	48.9	37.6	.02
Renal insufficiency,	4.0	3.0	.57
Family history of CAD	31.9	32.9	.83
History of PCI	44.4	40.3	.37
History of CABG	7.1	6.5	.79
History of MI	31.1	32.5	.76
Charlson comorbidity index	1.5 \pm 1.8	1.3 \pm 1.6	.39
Vessels diseased (LM included)	2.3 \pm 0.5	2.3 \pm 0.5	.16
Number of vessels diseased (LM included)			.15
2	75.1	69.3	
3	23.6	28.6	
4	1.3	2.2	
Vessels treated	1.4 \pm 0.5	1.4 \pm 0.6	.87
Number of vessels treated			.76
1	59.6	59.3	
2	39.1	38.1	
3	1.3	2.6	
SYNTAX score	12.7 \pm 8.7	12.3 \pm 7.6	.91

Note. Values represent either mean \pm SD or % of per patient calculation. Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual anti-platelet therapy; LM, left main coronary artery; MI, myocardial infarction; (N)IDDM, (non) insulin-dependent diabetes mellitus; (N)STEMI, (non) ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

1-year ($p = .29$; Table 4) and 10.2 versus 13.4% at 5 years ($p = .29$; Table 5) in BP-SES and PP-EES arm, respectively (Figure 2). The TVF composite endpoint rates were similar in two arms at 1- and 5-years, as was the incidence of clinically indicated TLR at both time points (Tables 4 and 5). The incidence of all non-TVR and any revascularization was significantly higher in PP-EES arm only at 1-year follow-up (Tables 4 and 5). Rates of cardiac death, MI and definite or

TABLE 2 Baseline lesion and procedural characteristics

	BP-SES $n_{\text{patients}} = 225$ $n_{\text{lesions}} = 364$	PP-EES $n_{\text{patients}} = 231$ $n_{\text{lesions}} = 374$	p Value
Lesions detected	3.1 ± 1.5	3.1 ± 1.3	.57
Lesions treated	1.6 ± 0.8	1.6 ± 0.8	.93
Lesion location			.80
RCA	30.5	32.4	
LAD	37.9	34.2	
CFX	28.3	30.8	
LM	2.5	2.4	
Graft	0.8	0.3	
Ostial	7.5	9.9	.24
Calcification			.32
None/mild	76.2	81.8	
Moderate	16.1	11.6	
Severe	7.8	6.6	
Thrombus present	3.7	3.9	.93
Bifurcation	14.8	10.7	.09
CTO	2.2	0.3	.02
ACC/AHA classification			.14
A	3.5	2.8	
B1	12.1	16.9	
B2	48.9	49.7	
C	35.6	30.7	
Access site			.77
Radial	69.8	68.4	
Femoral	28.9	30.3	
Brachial	1.3	1.3	
Pre-dilatation	76.1	76.2	.97
Post-dilatation	51.0	49.5	.68
Stents implanted per patient	1.9 ± 1.0	2.0 ± 1.1	.30
Total implanted stent length per patient, mm	36.5 ± 20.1	37.5 ± 22.4	.93
Delivery success per stent	98.3	99.4	.15
Procedure success	97.3	97.8	.73

Note. Values represent either mean ± SD or % of either per patient or per lesion calculation.

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; CFX, left circumflex coronary artery; CTO, chronic total occlusion; LAD, left anterior descending coronary artery; LM, left main coronary artery; RCA, right coronary artery.

probable ST, both at mid- and long-term follow-up were alike (Tables 4 and 5). Notably, the rate of very late ST (0.4%) was identical in two study arms (Table 5). The composite safety endpoints of cardiac death and MI and POCE during follow-up are presented in Figures 3 and 4. At 5-years, rate of cardiac death and MI was 6.7% in BP-SES arm compared to 10.8% in PP-EES arm ($p = .12$; Table 5). Five-year rates of POCE were 27.1% in BP-SES versus 34.2% in PP-EES ($p = .10$; Table 5).

TABLE 3 Dual antiplatelet therapy

	BP-SES $n = 225$	PP-EES $n = 231$	p Value
DAPT at 1 month	97.8 (218/223)	98.7 (227/230)	.45
DAPT at 4 months	96.4 (215/223)	96.9 (222/229)	.75
DAPT at 9 months	85.4 (187/219)	85.0 (187/220)	.91
DAPT at 1 year	65.6 (143/218)	62.7 (138/220)	.53
DAPT at 2 years	29.9 (64/214)	24.4 (52/213)	.20
DAPT at 3 years	20.6 (43/209)	16.9 (35/207)	.34
DAPT at 4 years	17.1 (35/205)	14.1 (29/206)	.40
DAPT at 5 years	15.0 (30/200)	13.9 (28/201)	.76

Note. Values represent % (number) of patients on DAPT at a given follow-up time-point.

Abbreviation: DAPT, dual antiplatelet therapy.

At 1 year follow-up, no difference in bleeding rate between the two groups was noted (Table 4), however, a statistically significant higher rate of bleeding incidence at 5-years follow-up was observed in BP-SES arm (Table 5). Finally, the analysis of possible predictors of TLF, including diabetes, Charlson comorbidity index, Syntax score, and complete versus incomplete revascularization of the coronary tree is shown in Figure 5. The risk of TLF after treatment with BP-SES compared with PP-EES did not differ across categories of these predictors (p for interaction $>.05$).

4 | DISCUSSION

To the best of our knowledge, the presented data represents unique clinical evidence of long-term safety and efficacy of a bioresorbable polymer coated sirolimus-eluting stent in the treatment of high risk MVD patients. This prespecified substudy of the CENTURY II randomized controlled trial demonstrates a good 5-year performance, both for bioresorbable (BP-SES) and permanent polymer (PP-EES) system. This is evidenced by similarly low rates of composite clinical outcomes, like TLF (10.2 vs. 13.4%; $p = .29$), TVF (14.2 vs. 14.7%; $p = .88$), cardiac death and MI (6.7 vs. 10.8%; $p = .12$), and POCE (27.1 vs. 34.2%; $p = .10$) up to 5 years follow-up, in two study arms, respectively. Moreover, relatively low and comparable TLR, TVR, cardiac death, MI, and definite or probable ST rates, alongside remarkably low (0.4%) very late ST in both treatment arms, add to the overall excellent long-term safety and efficacy profile of the two investigated devices. Although in our study, we observed less non-TVR in BP-SES versus PP-EES at both 1 year (1.8 vs. 7.4%; $p = .005$) and 5 years follow-up (8.4 vs. 14.3%; $p = .05$), this most likely reflects the progression of coronary artery disease itself rather than the actual difference in efficacy between the two compared devices.

Nowadays coronary artery stenting is increasingly being used to treat the high-risk coronary artery disease patients. Therefore, the evidence of safety and efficacy benefits of different new-generation DES systems is needed. The clinical performance and potential benefits of bioresorbable and permanent (second-generation) drug-carriers has been subjected to scrutiny in numerous studies. While both systems have been shown to

TABLE 4 Clinical outcomes at 1-year follow-up

	BP-SES n = 225	PP-EES n = 231	p Value
All cause death	2.7 (6/225)	2.6 (6/231)	.96
Cardiac death	2.2 (5/225)	1.3 (3/231)	.45
All MI	2.7 (6/225)	3.5 (8/231)	.62
TV-related MI	1.3 (3/225)	2.2 (5/231)	.50
Clinically indicated revascularization			
Any revascularization	5.8 (13/225)	9.5 (22/231)	.13
TLR	2.2 (5/225)	3.9 (9/231)	.30
TVR	4.9 (11/225)	5.2 (12/231)	.88
Non-TVR	1.3 (3/225)	4.3 (10/231)	.05
All revascularizations			
Any revascularization	7.6 (17/225)	13.9 (32/231)	.03
TLR	3.1 (7/225)	4.3 (10/231)	.49
TVR	6.2 (14/225)	6.9 (16/231)	.76
Non-TVR	1.8 (4/225)	7.4 (17/231)	.005
Composite endpoints			
TLF	5.3 (12/225)	7.8 (18/231)	.29
TVF	8.0 (18/225)	9.1 (21/231)	.68
Cardiac death and MI	4.9 (11/225)	4.8 (11/231)	.95
POCE	12.0 (27/225)	18.2 (42/231)	.07
Stent thrombosis			
Total	0.4 (1/225)	1.3 (3/231)	.33
Definite	0.4 (1/225)	1.3 (3/231)	.33
Probable	0.0 (0/225)	0.0 (0/231)	–
Possible	0.0 (0/225)	0.0 (0/231)	–
Definite or probable	0.4 (1/225)	1.3 (3/231)	.33
Bleeding or vascular complications			
Any bleeding	7.6 (17/225)	9.5 (22/231)	.45
Bleeding BARC type 2–5	4.9 (11/225)	5.6 (13/231)	.72
Bleeding BARC type 3–5	1.8 (4/225)	1.7 (4/231)	.97

Note. Values represent % (number); BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; TLR, target lesion revascularization; TLF, target lesion failure, defined as composite of cardiac death, TV-related MI and clinically indicated TLR; TV, target vessel; TVF: target vessel failure, defined as composite of cardiac death, TV-related MI and clinically indicated TVR; TVR, target vessel revascularization; POCE, patient oriented composite endpoint defined as any death, any MI and any coronary revascularization.

associate with better outcomes than first-generation DES,^{12,13} in recent years, it has been debated if their long-term clinical performance is comparable or different, and if distinct, in which context benefits can be achieved, as to provide indication for the use of one over the other system.¹⁴

To this end, a consensus is emerging that BP-DES are not inferior and, in some contexts, may even be more beneficial, than their contemporary PP-DES counterparts. This notion, for example, includes reports of more favorable clinical outcomes of BP-DES in high-risk STEMI patients.¹⁵ The caution, however, needs to be taken when

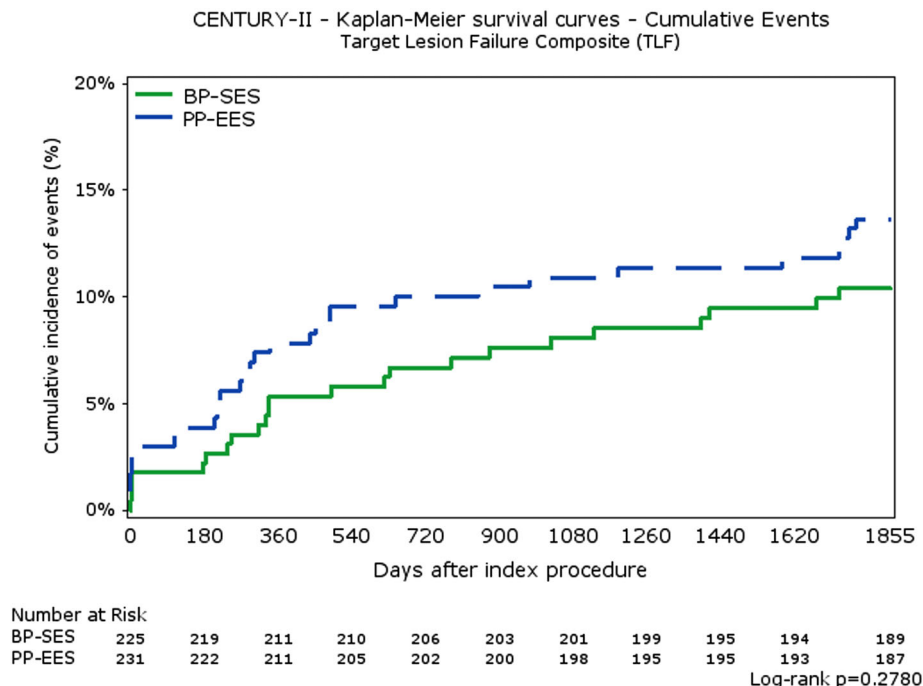
TABLE 5 Clinical outcomes at 5-year follow-up

	BP-SES n = 225	PP-EES n = 231	p Value
All cause death	9.3 (21/225)	10.8 (25/231)	.60
Cardiac death	4.0 (9/225)	5.2 (12/231)	.54
All MI	3.1 (7/225)	5.6 (13/231)	.19
TV-related MI	1.3 (3/225)	2.6 (6/231)	.33
Clinically indicated revascularization			
Any revascularization	13.3 (30/225)	13.4 (31/231)	.98
TLR	6.2 (14/225)	6.1 (14/231)	.94
TVR	10.2 (23/225)	7.8 (18/231)	.37
Non-TVR	4.9 (11/225)	6.9 (16/231)	.36
All revascularizations			
Any revascularization	17.8 (40/225)	22.5 (52/231)	.21
TLR	8.4 (19/225)	6.9 (16/231)	.54
TVR	13.3 (30/225)	11.3 (26/231)	.50
Non-TVR	8.4 (19/225)	14.3 (33/231)	.05
Composite endpoints			
TLF	10.2 (23/225)	13.4 (31/231)	.29
TVF	14.2 (32/225)	14.7 (34/231)	.88
Cardiac death and MI	6.7 (15/225)	10.8 (25/231)	.12
POCE	27.1 (61/225)	34.2 (79/231)	.10
Stent thrombosis			
Total	0.9 (2/225)	1.7 (4/231)	.43
Definite	0.9 (2/225)	1.7 (4/231)	.43
Probable	0.0 (0/225)	0.0 (0/231)	–
Possible	0.0 (0/225)	0.0 (0/231)	–
Definite or probable	0.9 (2/225)	1.7 (4/231)	.43
Stent thrombosis (definite or probable)			
Acute	0.0 (0/225)	0.0 (0/231)	–
Subacute	0.0 (0/225)	0.9 (2/231)	.16
Late	0.4 (1/225)	0.4 (1/231)	.99
Very late	0.4 (1/225)	0.4 (1/231)	.99
Bleeding or vascular complications			
Any bleeding	22.2 (50/225)	15.6 (36/231)	.07
Bleeding BARC type 2–5	19.6 (44/225)	11.7 (27/231)	.02
Bleeding BARC type 3–5	15.1 (34/225)	7.8 (18/231)	.01
Bleeding BARC type 3–5	6.7 (15/225)	2.6 (6/231)	.04

Note. Values represent % (number); BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; TLR, target lesion revascularization; TLF, target lesion failure, defined as composite of cardiac death, TV-related MI and clinically indicated TLR; TV, target vessel; TVF, target vessel failure, defined as composite of cardiac death, TV-related MI and clinically indicated TVR; TVR, target vessel revascularization; POCE, patient oriented composite endpoint defined as any death, any MI and any coronary revascularization.

comparing the performance of various BP- and PP-DES, as due to specific design differences, they might need to be compared as separate device entities, rather than as members of larger device families. Indeed, in their systematic review and network meta-analysis of

FIGURE 2 Kaplan–Meier curves of cumulative event rates of target lesion failure (TLF) composite endpoint, up until 5-year follow-up. BP-SES, bioresorbable polymer sirolimus-eluting stent; PP-EES, permanent polymer everolimus-eluting stent [Color figure can be viewed at wileyonlinelibrary.com]



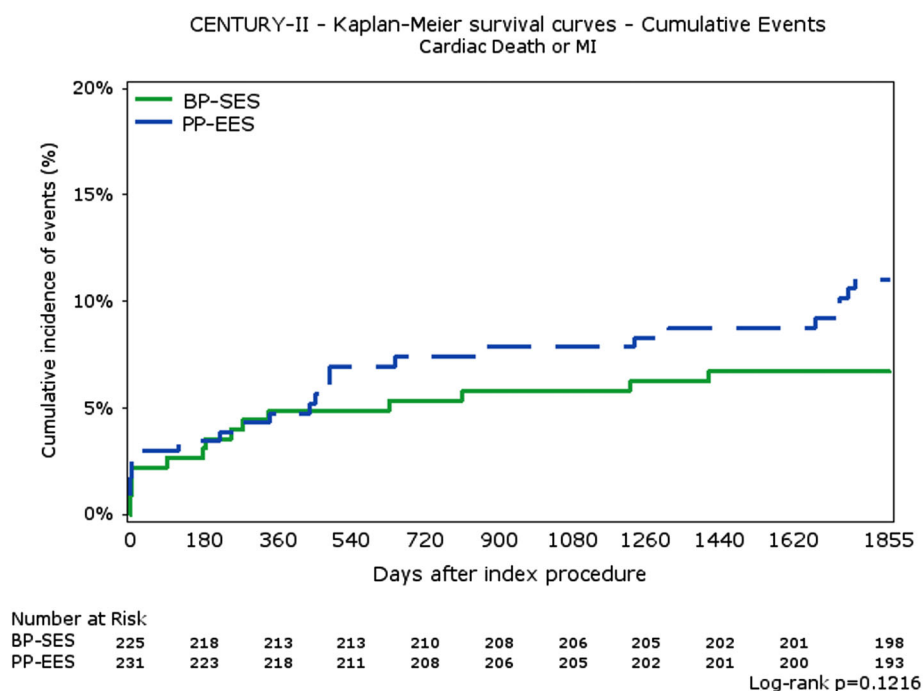
113 trials (90,584 patients), comparing the clinical performance of bare metal, bioresorbable-polymer, and permanent-polymer stent systems, Kang et al. concluded that not only the features of a particular polymeric carrier itself, but also specific stent alloy and design aspects, as well as the strut thickness and the used drug, all combined, may determine the safety of a particular DES system.¹⁶

A short bio-resorption time of the drug-eluting polymer, following stent implantation, should theoretically provide benefits in terms of late adverse safety events. Nevertheless, a recent meta-analysis of 16 randomized clinical trials (19,886 patients), comparing safety and efficacy of BP-DES and the second-generation PP-DES systems, reached a

conclusion that both have comparable safety and efficacy profiles.¹⁷

Consistently, a recent 5-year follow-up reports of the COMPARE II and NEXT trials, in which bioresorbable polymer, biolimus-eluting Nobori stent was compared to the second-generation everolimus-eluting PP-DES, found no significant differences in relevant safety and efficacy endpoints, neither at short nor at mid- to long-term follow-up.^{18,19} While these findings raise questions, whether expected long-term safety benefits of the BP-DES over PP-DES devices are indeed achievable, further independent trials are needed to evaluate their performance, not only in general, but also in specific, more demanding patient populations.

FIGURE 3 Kaplan–Meier curves of cumulative event rates of cardiac deaths and myocardial infarction (MI) composite endpoint, up until 5-year follow-up. BP-SES, bioresorbable polymer sirolimus-eluting stent; PP-EES, permanent polymer everolimus-eluting stent [Color figure can be viewed at wileyonlinelibrary.com]



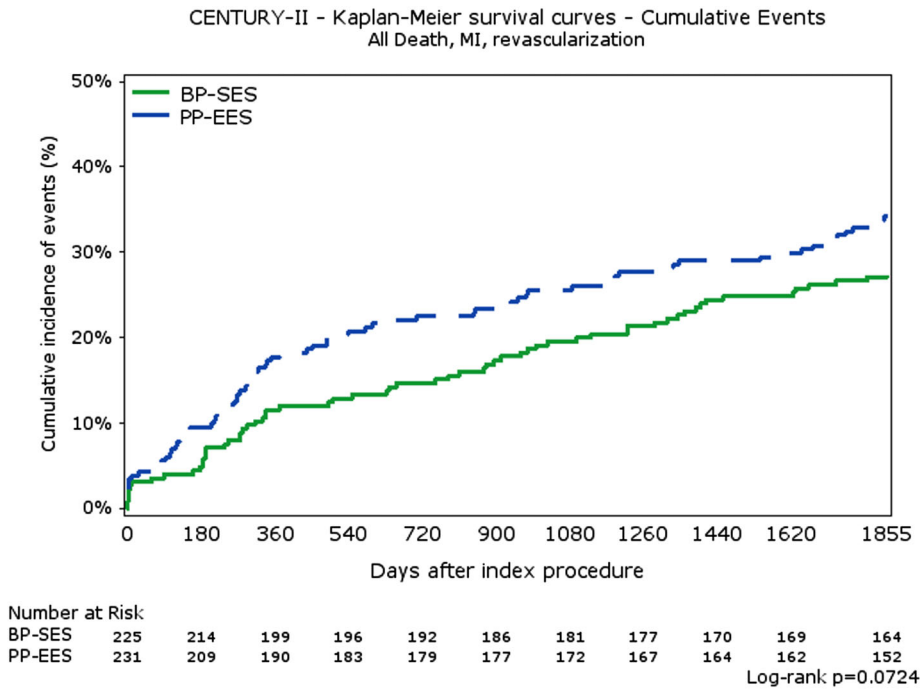


FIGURE 4 Kaplan-Meier curves of cumulative event rates of patient-oriented composite endpoint (POCE), up until 5-year follow-up. BP-SES, bioresorbable polymer sirolimus-eluting stent; PP-EES, permanent polymer everolimus-eluting stent [Color figure can be viewed at wileyonlinelibrary.com]

To this end, it is known that treatment of MVD patients poses a significant challenge for the contemporary PCI practice, as they associate with worse clinical prognosis. Findings of the present study demonstrate excellent mid- to long-term safety and efficacy of the studied Ultimaster DES in terms of several key clinical outcomes. This data complements earlier findings of the DISCOVERY 1TO3 trial, where 60 MVD patients were treated with the same DES and nearly complete strut coverage was noted very early after the initial stent implantation (within 1–3 months).²⁰ This positive biological response implied a possibility that Ultimaster BP-SES system could provide beneficial clinical outcomes in this high-risk patient population. Coupled with the hypothesis-generating findings of the present study, these observations

warrant further investigation through dedicated, sufficiently powered trials. Overall, the present study adds to the numerous published evidence from recent years on excellent performance of Ultimaster (BP-SES) system. This includes reports of favorable outcomes in general^{8,9} and specific subpopulations, like STEMI patients,²¹ bifurcations,²² long lesions,²³ and small vessels.²⁴

Our analysis of TLF predictors implies that patient, lesion, and procedural complexity exert little impact on TLF in the studied context (Figure 5). Particularly interesting is that relative risk of TLF does not seem to be impacted by the decision to perform complete over incomplete coronary tree revascularization. This finding is at odds with current trends, favoring the complete approach as the more

Subgroup Analysis

Outcome: Target Lesion Failure Composite (TLF) (5Y)

Relative Risk with 95% CI, number of events / Nr of subjects, p-values

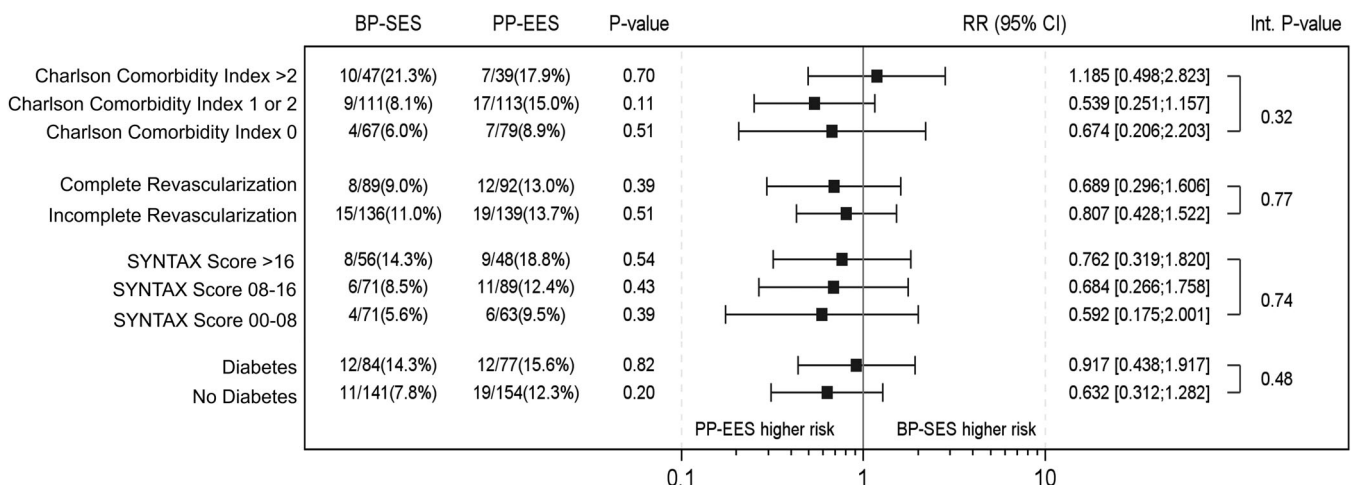


FIGURE 5 Predictors of target lesion failure (TLF): relative risk with 95% confidence interval (CI) of TLF at 5 years. Int. p -value: p -value for interaction

optimal *modus operandi*. Potential explanation could be that physiological assessment of stenosis in untreated vessels was determining factor for deferring revascularization, leading as such to similar outcomes. Caution, however, needs to be taken with interpretation of these findings, as they derive from a relatively small study subset of patients and as such warrant further analysis.

Finally, bleeding rates were comparable at 1 year follow up while a higher cumulative bleeding incidence was noted in BP-SES treated MVD patients at 5 years. Considering no difference in DAPT use over the 5-year follow-up period, a possible explanation can be that higher proportion of patients with high-risk for bleeding, including prevalence of oral anticoagulant users, patients with traumas, and/or comorbidities was acquired through 5 years follow-up in the BP-SES group.

5 | LIMITATIONS

Although MVD patients did constitute a balanced, predefined subgroup of the CENTURY II trial, this substudy was not powered to demonstrate non-inferiority of BP-SES to PP-EES. Therefore, herein presented results are only hypothesis-generating and future studies, with sufficient power, are needed to corroborate these interesting findings. Also notable is that the angiographic complexity of MVD patient in this CENTURY II substudy was relatively low (with baseline SYNTAX score between 12 and 13 for both groups). Therefore, our results cannot be extrapolated to all MVD patients seen in everyday practice, that are treated by either PCI or CABG. Moreover, even though DMC and CEC members were blinded for patients' assignment, logistical factors prevented blinding of study personnel. While this factor certainly warrants caution, we believe that its impact on reported findings should not be significant, as to cast doubt on the overall conclusions of the study.

6 | CONCLUSION

Our study reveals, that throughout the 5-year follow-up period, sirolimus-eluting bioresorbable polymer Ultimaster stent (BP-SES), displays similarly good long-term safety and efficacy profile as the everolimus-eluting permanent polymer Xience stent (PP-EES), in the treatment of MVD patients.

ACKNOWLEDGMENTS

The authors would like to express their utmost gratitude to all CENTURY II study investigators who actively contributed in meticulous data collection process for this trial.

CONFLICT OF INTEREST

Except for the research grant received within the framework of the CENTURY II study, the authors have no conflict of interest to declare.

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How to cite this article: Iñiguez A, Chevalier B, Richardt G, et al. Comparison of long-term clinical outcomes in multivessel coronary artery disease patients treated either with bioresorbable polymer sirolimus-eluting stent or permanent polymer everolimus-eluting stent: 5-year results of the CENTURY II randomized clinical trial. *Catheter Cardiovasc Interv*. 2020;95:175-184. <https://doi.org/10.1002/ccd.28224>